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PATENT
Attorney Docket No. 175931

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Mitchell et al.

Application No. 09/424,519

Art Unit: 1614

Examiner: Kwon, B.

Filed: March 3, 2000

For: THE USE OF A NITROXIDE OR A PRODRUG THEREOF IN THE PROPHYLACTIC AND THERAPEUTIC TREATMENT OF CANCER

TRANSMITTAL OF APPELLANTS' APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In accordance with 37 CFR 1.192, appellants hereby submit Appellants' Brief on Appeal in triplicate.

The items checked below are appropriate:

1. Status of Appellants

This application is on behalf of ☒ other than a small entity or ☐ a small entity.

The verified statement ☐ is attached or ☐ was filed on .

2. Fee for Filing Brief on Appeal

Pursuant to 37 CFR 1.17(e), the fee for filing the Brief on Appeal is for: ☒ other than a small entity or ☐ a small entity.

Brief Fee Due $320.00

3. Oral Hearing

☐ Appellants request an oral hearing in accordance with 37 CFR 1.194.

CERTIFICATE OF MAILING

I hereby certify that this document (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: June 17, 2002 Catherine M. Cioffi

4. **Extension of Time**

☒ Appellants petition for a three-month extension of time under 37 CFR 1.136, the fee for which is $920.00.

☐ Appellants believe that no extension of time is required. However, this conditional petition is being made to provide for the possibility that appellants have inadvertently overlooked the need for a petition and fee for extension of time.

Extension fee due with this request: $920.00

5. **Total Fee Due**

The total fee due is:

Brief on Appeal Fee	$320.00
Request for Oral Hearing	$ 0.00
Extension Fee (if any)	$920.00

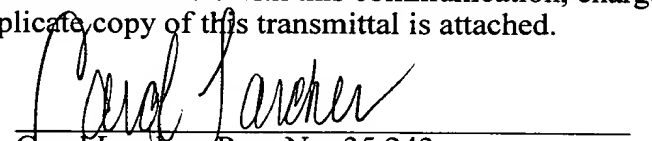
Total Fee Due: $1,240.00

6. **Fee Payment**

☒ Attached is a check in the sum of $1,240.00.
☐ Charge Account No. 12-1216 the sum of $. A duplicate of this transmittal is attached.

7. **Fee Deficiency**

☒ If any additional fee is required in connection with this communication, charge Account No. 12-1216. A duplicate copy of this transmittal is attached.



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Date: June 17, 2002

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PATENT
Attorney Docket No. 175931

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Mitchell et al.

Application No. 09/424,519

Filed: March 3, 2000

Group Art Unit: 1614

Examiner: Kwon, B.

For: THE USE OF A NITROXIDE OR A PRODRUG THEREOF IN THE PROPHYLACTIC AND THERAPEUTIC TREATMENT OF CANCER

APPELLANTS' BRIEF ON APPEAL

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The following comprises Appellants' Brief on Appeal in support of the appeal of the decision of the Examiner of Group Art Unit 1614 per the final Office Action dated May 24, 2001, and the Advisory Action dated October 24, 2001. The Notice of Appeal was filed on November 26, 2001, and was received by the United States Patent and Trademark Office on January 16, 2001, thereby making the appeal brief due on March 16, 2001. This Appeal Brief is timely since it is accompanied by a three-month extension of time for filing a brief under 37 C.F.R. § 1.136(a).

1. REAL PARTY IN INTEREST

The real party in interest is the government of the United States of America as represented by the Secretary, Department of Health and Human Services.

2. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any appeals or interferences that will directly affect or be affected by or have a bearing on the Board's decision in this appeal.

3. STATUS OF CLAIMS

Claims 1-3 and 22-27 are currently pending, are the subject of this appeal, and are set forth in the Appendix attached hereto.

4. STATUS OF AMENDMENTS

No amendment was filed subsequently to final rejection.

5. SUMMARY OF INVENTION

The appealed claims are directed to a method of preventing or treating cancer in an animal (e.g., page 3, line 18, through page 5, line 29). The method comprises administering to the animal a nitroxide (e.g., compounds of Formula I or II) or prodrug thereof in an amount sufficient to prevent or treat the cancer. Additional appealed claims are directed towards the above-described method in which the cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene (e.g., p53 gene) (e.g., page 7, lines 9-23).

6. ISSUES

The issues on appeal are as follows:

(i) whether or not claims 1-3 are anticipated by Monti et al. (*PAACR Annual Meeting 36*:387, Abstract 2304 (March 1995)) ("Monti I"); and

(ii) whether or not claims 24-27 are obvious in view of and, therefore, unpatentable over, Monti et al. (*PAACR Annual Meeting 38*:193, Abstract 1298 (March 1997)) ("Monti II") in view of Harris (*J. Nat'l Cancer Inst. 88*:1442-1455 (1996)) ("Harris"). Appellants point out that the Examiner never rejected claims 22 and 23 under Section 103. Appellants have assumed, for purposes of this appeal brief, that these claims are also rejected but request that the Examiner clarify the rejection in this regard for purposes of establishing a complete record.

7. GROUPING OF CLAIMS

The rejected claims consist of two claim groups. Group I consists of claims 1-3, which are directed to a method of preventing or treating cancer in an animal by administering a nitroxide or prodrug thereof. Group II consists of claims 22-27, which are directed to a method of preventing or treating cancer in an animal by administering a nitroxide or prodrug thereof. The cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene (e.g., p53 gene). The claims do not stand or fall together inasmuch as claims 24-27 [sic--22-27?] are directed to cancer that is due to a genetic defect, claims 24-27 [sic--22-27?] are not subject to the anticipation rejection of claims 1-3, and claims 1-3 are not subject to the obviousness rejection of claims 24-27 [sic--22-27?].

The claims within Group I (i.e., claims 1-3) do not stand or fall together. The prior art does not teach the use of a nitroxide or prodrug thereof to prevent or treat cancer in an animal as specified in claim 1. In addition, the prior art does not teach the use of an alicyclic or heterocyclic nitroxide or prodrug thereof to prevent or treat cancer in an animal as recited in claim 2. The prior art also does not teach the elements of claim 3, namely the use of a

compound of Formula I or II to prevent or treat cancer in an animal. In the event that the prior art was found to teach or suggest the use of a nitroxide or prodrug thereof to prevent or treat cancer, such a teaching or suggestion would not necessarily constitute a teaching of the use of an alicyclic or heterocyclic nitroxide or prodrug thereof (as specified in claim 2) or the use of a compound of Formula I or II (as specified in claim 3).

The claims within Group II (i.e., claims 22-27) do not stand or fall together. The prior art does not teach or suggest the use of a nitroxide or prodrug thereof to prevent or treat cancer in an animal, in which the cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene as specified in claim 22. In particular, the prior art does not teach or suggest such a method in which the tumor suppressor gene is the p53 gene (claim 23). The prior art does not teach or suggest the use of an alicyclic or heterocyclic nitroxide or prodrug thereof to prevent or treat cancer in an animal, in which the cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene as recited in claim 24. In addition, the prior art does not teach or suggest such a method in which the tumor suppressor gene is the p53 gene (claim 25). The prior art does not teach the elements of claim 26, namely the use of a compound of Formula I or II to prevent or treat cancer in an animal, in which the cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene. Moreover, the prior art does not teach or suggest such a method in which the tumor suppressor gene is the p53 gene (claim 27). In the event that the prior art was found to teach or suggest the use of a nitroxide or prodrug thereof to prevent or treat cancer, the same prior art would not necessarily teach or suggest the use of an alicyclic or heterocyclic nitroxide or prodrug thereof (as specified in claim 24) or the use of a compound of Formula I or II (as specified in claim 26).

8. ARGUMENT

Discussion of the Rejection Under 35 U.S.C. § 102(b)

According to the Examiner, claims 1-3 of the instant application are anticipated by Monti I because, allegedly, the claimed prophylactic use of nitroxides to prevent cancer in an animal is inherently disclosed by Monti I. Monti I summarily states that "Tempol ... was recently reported to act as radioprotector in mice." The Examiner contends that "[i]t is now well settled law that administrating compounds inherently possessing a protective utility anticipates claims directed to such protective use." (Office Action issued May 24, 2001, page 4, second full paragraph). Despite the Examiner's contention that this is "well settled law," the Examiner cites no legal authority for this alleged precedent. Indeed, Appellants can find no law asserting such a broad expansion of the inherency doctrine.

Anticipation by inherency is a narrow doctrine with limited application. A reference is anticipatory only if it discloses every limitation of the claimed invention either explicitly or

inherently. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346, 51 USPQ2d 1943, 1945 (Fed. Cir. 1999). A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (citations omitted). To establish inherency, the Federal Circuit has held that "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999) (citations omitted). In other words, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). In this case, it is clear that the Examiner has proffered no evidence that, in view of Monti I, the natural result flowing from administration of nitroxides is the prevention of cancer.

The fact that an agent may act as a radioprotector does not necessarily mean that the compound can be used to treat cancer prophylactically. More is required to show anticipation by inherency. *Ex parte Levy*, 17 USPQ2d at 1464 (holding that the Examiner must provide factual or technical reasoning). Inherency may not be established by mere probabilities or possibilities. *Robertson*, 169 F.3d at 745, 49 USPQ2d at 1950-51. To establish inherency, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* In view of Monti I, the mere possibility or probability that radioprotectors may prevent cancer is not sufficient to establish inherency.

Furthermore, the doctrine of anticipation by inherency places a lower bar on claims directed to method claims, as compared to claims directed to compounds and compositions. A claim directed to a novel use of a known composition is still patentable. *See, In re Schoenwald*, 964 F.2d 1122, 1124, 22 USPQ2d 1671, 1673 (Fed. Cir. 1992) (holding that a compound claim to an ophthalmic composition to treat dry eye syndrome is not patentable in view of prior art but a method of treatment claimed in the parent application is proper). The claimed method of prophylactically or therapeutically treating cancer, as a novel property of the nitroxide compound disclosed, is, therefore, patentable as a method claim, independent of knowledge of the composition in the prior art and in the absence of evidence that the claimed function was already known in the art. As the Examiner has not adequately demonstrated that the use of Tempol for the prevention of cancer is inherent to its description in the prior art as a radioprotective agent, the Examiner has failed to meet his burden of showing that Monti I anticipates claims 1-3 of the instant application under the narrow doctrine of anticipation by inherency.

While cancer is one possible result of exposure to radiation, the two are not mutually inclusive. It is well-known that exposure to radiation can lead to many disease states other

than cancer (e.g., uterine myoma, chronic hepatitis, liver cirrhosis, cataracts, altered immune functions, circulatory disease, digestive disease, etc.) *See, e.g.*, Wong et al., *Radiation Research, 135*, 418-430 (1993). Also, an animal may have cancer as a result of sources other than radiation, such as a genetic defect or exposure to a non-radioactive carcinogen. Gleaned from the Examiner's reasoning is that any compound capable of acting as a radioprotector necessarily acts to protect against these other disease states, e.g., cataracts and cancer caused by non-radioactive means, such as, for example, a genetic defect. Clearly, the Examiner's reasoning is nothing more than mere conjecture. *See, e.g., W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1554, 220 USPQ 303, 314 (Fed. Cir. 1983) ("Anticipation ... cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.").

Even assuming, for the sake of argument, that prevention of cancer does flow naturally from radioprotection, Monti I still does not anticipate claims 1-3 of the instant application because Monti I does not enable the invention. A reference cannot anticipate that which it does not enable. *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) (in order to anticipate, "the [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it"). The Examiner's reliance on *Ex parte Novitski* does not diminish the enablement requirement. In *Novitski*, the prior art reference fully enabled the invention claimed in the application rejected by the Examiner. 26 U.S.P.Q.2d 1389 (Bd. Pat. App. & Int. 1993) (concluding that if the authors of the prior art reference, *having taken the manipulative steps described in the reference* of inoculating plants with a particular bacteria, had then attempted to measure for the results described by the inventor of nematode inhibition, the authors of the prior art reference would have necessarily uncovered it) (emphasis added). Hence, in order to anticipate, Monti I must describe the claimed invention sufficiently to have placed a person of ordinary skill in the art in possession of the invention.

Monti's mere conclusory statement that Tempol has been found to act as a radioprotector in mice does not, in and of itself, teach or suggest, and hence does not enable, a method of using a nitroxide, or a prodrug thereof, for the prophylactic or therapeutic treatment of cancer in an animal. Monti I provides no teaching whatsoever regarding nitroxides in the prophylaxis of cancer, such as *in vivo* activity, suitable doses, formulation, modes of administration and types of cancer. Nor does Monti I provide a working example or any experimental data regarding the effectiveness of nitroxides in the treatment of cancer in an animal. Absent these teachings, Monti I cannot anticipate claims 1-3 of the instant application. To conclude otherwise would require the Examiner to use the instant specification as a blueprint to construct his anticipation rejection, resulting in an impermissible use of hindsight. *See, e.g., Rowe v. Dror*, 112 F.3d 473, 478, 480-81, 42 USPQ2d 1550, 1553, 1555 (Fed. Cir. 1997) (in regards to anticipation by inherency, "[a]bout

the most that can be said for the [prior art] patent is that it does not explicitly describe anything inconsistent with [the claimed] procedures. However, this negative pregnant is not enough to show anticipation."); *In re Newell*, 891 F.2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989) ("[A] retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination.")

In view of the above, Appellants submit that claims 1-3 are not anticipated by Monti I. Therefore, this rejection should be reversed.

Discussion of the Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 24-27 (and presumably claims 22 and 23 as well) as obvious in view of, and, therefore, unpatentable over Monti II in view of Harris. Monti II, however, studied *in vitro* the mutagenic and cytotoxic effects of Tempol against DNA repair-deficient bacterial strains. Monti II does nothing more than suggest that similar effects *might* be observed in an *in vitro* study of tumor cell lines. There is no teaching or suggestion in Monti II of a method of using a nitroxide, or a prodrug thereof, to treat cancer in an animal prophylactically or therapeutically as taught by the present invention. The Examiner attempts to cure the deficiencies of Monti II by alleging that "[i]t is old and well known in the art to employ an agent that is effective in vitro study into vivo study to monitor its efficacy." See, Office Action issued May 24, 2001, page 5 (underlines original). In doing so, the Examiner has applied the wrong standard in assessing obviousness. That "monitoring the efficacy" of a compound *in vivo* may be old and well-known does not, in and of itself, constitute a teaching or suggestion to use a nitroxide (or a prodrug thereof) in the prophylactic and therapeutic treatment of cancer, particularly when the primary reference, itself, does not extrapolate from the effects observed for tumor cell lines *in vitro* to efficacy *in vivo*. The Examiner concludes that a demonstration of *in vitro* efficacy at the time of filing of the instant application would have been viewed as reasonably predictive of *in vivo* results. However, simply because a compound gives positive results *in vitro*, it does not necessarily follow that there is a reasonable probability of success for prophylactic or therapeutic use of the compound *in vivo*. *In re Carroll*, 601 F.2d 1184, 1186, 202 USPQ 571, 572-573 (CCPA 1979). *In vitro* activity of a compound is not necessarily predictive of its activity *in vivo* or its effectiveness as a therapeutic or prophylactic agent, due to the complexity of biological systems. In other words, one simply cannot equate the controlled conditions of a buffered solution or a cell-derived solution with the complex environment inside and outside a cell, tissue or organ in an animal.

Monti II simply does not motivate the ordinarily skilled artisan to use a nitroxide (or prodrug thereof) in the prophylactic or therapeutic treatment of cancer in an animal, let alone

teach or suggest such a use. Monti II also does not provide an ordinarily skilled artisan with a reasonable expectation of success.

For a claim to be obvious, the prior art must provide the ordinarily skilled artisan with a reasonable expectation of success of the claimed invention after modifications are made to the prior art. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1125, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000); *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985). That it would have been "obvious to try" the modification is not a sufficient basis on which to rest a determination of obviousness. *In re Merck*, 800 F.2d 1091,1097, 231 USPQ 375, 379 (Fed. Cir. 1986). In the art of cancer prophylaxis and treatment, an *in vitro* assay of a compound demonstrating anti-cancer properties provides little, if any, expectation of success that the compound will demonstrate anti-cancer properties *in vivo*. This uncertainty is similar to that found in *Ex Parte Balzarini*, in which the Board of Patent Appeals and Interferences found that an *in vitro* assay showing efficacy of a compound against HIV was insufficient to support a claim directed towards the *in vivo* use of the compound in the treatment of HIV. *Ex Parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. Int. 1991). The Board, in examining the state of the art indicated, "*in vitro* testing of the type performed in the present specification is useful as a screening tool of *potential* anti-viral agents in the fight against AIDS, but any conclusion as to whether a specific anti-viral compound will, in fact, be effective *in vivo* is not predictive from the *in vitro* tests." *Id.* at 1896. The art of cancer treatment and prophylaxis is similarly wrought with difficulties in translating the results of *in vitro* assays to positive *in vivo* results. As such, while an *in vitro* assay of tumor prophylaxis or treatment may provide a basis for a finding that it would be obvious to try the compound in an *in vivo* method, it provides no reasonable basis for an expectation of the successful use of the compound in the *in vivo* method.

The Examiner's citation of Harris as a secondary reference does not cure the deficiencies of the primary reference Monti II. The Examiner relies on Harris's disclosure that many cancers are a result of p53 mutations and that such cancers can be treated by inducing apoptosis. Yet, Harris states that promyelocytic HL-60 cells, the very cells utilized in the *in vitro* study in Monti II, are p53 null (page 9, line 23). It is also known in the art that myeloblastic KG1 cells, also used in the *in vitro* study in Monti II, are null for p53 expression as well. See Guillouf et al., *Oncogene*, *10*(11), 2263-2270 (1995), and Shimizu et al., *Exp. Cell Res. 226*(2), 292-301 (1996), the abstracts of which are enclosed herewith. Consequently, in contrast to the Examiner's allegation, one having ordinary skill in the art would not have been motivated to combine the teachings of Monti II and Harris.

Even assuming, for the sake of argument, that one of ordinary skill in the art would have been motivated to make such a combination, which Appellants maintain is not the case, one of ordinary skill in the art would not have arrived at the present invention. The combination of references does not result in the prophylactic or therapeutic treatment, both *in*

vivo processes, of a cancer that has a genetic defect of the p53 gene. As discussed above, Monti II does not teach the *in vivo* treatment of cancer, and the *in vitro* results that Monti II reports in no way reflect the *in vivo* environment of cells. The greatly increased complexity of an *in vivo* experiment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of the *in vitro* assay to a treatment in animals with any reasonable degree of predictability. In addition, the conclusions that Monti II draws based on the *in vitro* results are questionable. The observation of a block in the cell cycle with Tempol does not necessarily imply that apoptosis was induced. Furthermore, even if apoptosis was induced, induction of apoptosis does not necessarily translate into a treatment of cancer—either *in vitro* or *in vivo*. Apoptosis is simply programmed cell death that is needed to destroy cells that represent a threat to the organism. Apoptosis can occur in cells with DNA damage (e.g., cancer), cells with DNA damage that leads to birth defects, cells infected with viruses, including HIV, or cells affected by autoimmune diseases (e.g., lupus, rheumatoid arthritis). Assuming that Monti II's use of Tempol did induce apoptosis in HL60 and KG1 cell lines, these results, at best, might be construed as an invitation to experiment in an *in vivo* study. Again, as stated above, an invitation to experiment or "obvious to try" is most certainly *not* the legal standard used in determining obviousness (M.P.E.P. § 2145 X. B.). Moreover, Harris teaches that, if a cell undergoes apoptosis, it can occur via a p53-dependent pathway or a p53-*independent* pathway (see, for example, page 9, lines 19-23). As stated above, Harris and Guillouf teach that both HL60 and KG-1 cells do not express the p53 gene. If one of ordinary skill in the art indeed found the results of Monti II as an invitation to experiment, that artisan would likely only test cancers that were p53-null, since Monti II's cell lines did not express the p53 gene. Therefore, the ordinarily skilled artisan would not have arrived at the invention as defined by pending claims 22-27.

The Examiner (and Monti II as well) has made a series of leaps in logic and assumptions: namely that Tempol induces a block in the cell cycle *in vitro*, which induces apoptosis in cells *in vitro*, which implies treatment of a cancer *in vivo*, and since apoptosis occurred, it must imply that the cancer was due to a mutation in the p53 gene. Based on the disclosures of Monti II and Harris, this simply is not the case. To conclude otherwise would involve the benefit of impermissible hindsight vision afforded by the claimed invention. The Federal Circuit has emphasized that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing [i.e., actual evidence] of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617. The leaps in logic taken by the Examiner to support the obviousness rejection clearly demonstrate that an ordinarily skilled artisan, confronted with the same problems as the inventors and without

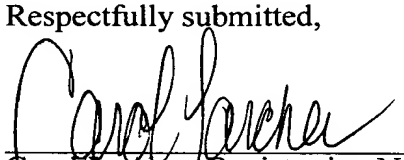
knowledge of the claimed invention, would not have had a reasonable expectation of success in obtaining the invention as defined in claims 22-27.

In view of the above, Appellants submit that claims 24-27 (and claims 22 and 23) are not obvious in view of Monti II and Harris. Therefore, this rejection should be reversed.

9. CONCLUSION

In view of the above, Appellants respectfully submit that the Examiner's rejections should be reversed.

Respectfully submitted,



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Date: June 17, 2002

CERTIFICATE OF MAILING

I hereby certify that this APPELLANTS' BRIEF ON APPEAL (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: June 17, 2002 Catherine M. Cioffi

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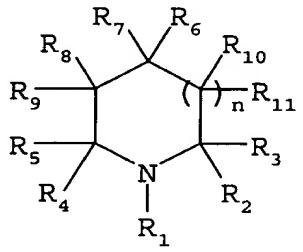
APPENDIX - PENDING CLAIMS ON APPEAL

1. A method for the prophylactic or therapeutic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer a nitroxide or a prodrug thereof in an amount sufficient to prevent or treat said cancer, wherein said cancer is susceptible to prevention or treatment by said nitroxide or prodrug thereof.

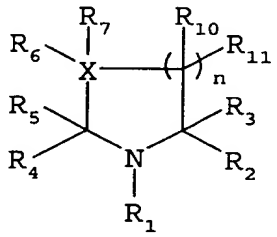
2. The method of claim 1, wherein said nitroxide or prodrug thereof is alicyclic or heterocyclic.

3. The method of claim 2, wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I

or



Formula II

wherein R_1 is selected from the group consisting of H, OH, OZ, O·, =O and Y, wherein Y is a leaving group, which can be converted to H, OH, O· or =O by reaction with a nucleophilic agent, and Z is selected from the group consisting of a $C_{1\text{-}20}$ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a $C_{1\text{-}20}$ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of a $C_{1\text{-}20}$ alkyl group, a $C_{2\text{-}20}$ alkenyl group, a $C_{2\text{-}20}$ alkynyl group, and $-CH_2-[CR'\ R'']_m-CH_3$, wherein R' is selected from the group consisting of hydrogen, a $C_{1\text{-}20}$ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R" is selected from the group consisting of hydrogen, a $C_{1\text{-}20}$ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a $C_{1\text{-}20}$ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein, $m \leq 30$, and R_2 and R_3 or R_4 and R_5 can be connected through one or more members, each of which is independently selected from the group consisting of carbon and a heteroatom,

wherein R_6, R_7, R_8 and R_9 are independently selected from the group consisting of hydrogen, a hydroxyl group, a C_{1-20} aldehydic group, a C_{1-20} keto group, a primary amino group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a sulfamato group, a metal-containing group, a silicone group, a halide, a C_{1-20} ester-containing group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a phosphonato group, a C_{1-20} alkyl group, a C_{2-20} alkenyl group, a C_{2-20} alkynyl group, and $-CH_2-[CR' R'']_m-CH_3$, wherein R' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R" is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, and $m \leq 30$, and wherein any one of R_6, R_7, R_8 and R_9 can be attached covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I, one of R_6 and R_7 and one of R_8 and R_9 can be absent such that a double bond joins the two carbon atoms to which the remaining R groups are attached, wherein n = 0-20 in Formula I, and n = 1-20 in Formula II, wherein X is a heteroatom, and wherein R_{10} and R_{11} are independently selected from the group consisting of a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} aliphatic/aromatic group, a heteroatomic group, a C_{1-20} ether-containing group, a C_{1-20} keto group, a C_{1-20} aldehydic group, a carboxamido group, a cyano group, an amino group, a carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato group, a sulfinato group, and a sulfonato group, and wherein R_{10} and R_{11} can be connected through an aliphatic group and/or an aromatic group, or R_{10} and/or R_{11} can comprise a member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a protein.

22. The method of claim 1, wherein said cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene.

23. The method of claim 22, wherein said tumor suppressor gene is the p53 gene.

24. The method of claim 2, wherein said cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene.

25. The method of claim 24, wherein said tumor suppressor gene is the p53 gene.

26. The method of claim 3, wherein said cancer is due to a genetic defect of a cancer regulatory gene or a tumor suppressor gene.

27. The method of claim 26, wherein said tumor suppressor gene is the p53 gene.

1: *Oncogene* 1995 Jun 1;10(11):2263-70

p53 involvement in control of G2 exit of the cell cycle: role in DNA damage-induced apoptosis.

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DNA damage in proliferating mammalian cells induces a complex cellular response comprising perturbation of the cell cycle and programmed cell death. The relationship between p53-dependent and p53-independent apoptotic cell death, as well as the cell cycle checkpoints induced by DNA damaging agents were explored in hematopoietic cells, using M1 myeloblastic leukemia cells, which are null for p53 expression, genetically engineered M1 variants, expressing p53ts and bcl-2 transgenes, as well as myeloblast enriched bone-marrow cells obtained from wild type p53 (wt p53) and p53-deficient mice. It is shown that gamma-irradiation of M1p53ts cells activated a function of the temperature sensitive mutant transgene p53 (p53ts), promoting increased apoptosis relative to parental, null p53 M1 cells. It is also shown that the kinetics of apoptotic cell death induced by gamma-irradiation correlated with the rapidity of exit from gamma-ray-induced G2 arrest for all the different hematopoietic cell types indicated above. Finally, data has been obtained to demonstrate that, in addition to a role in apoptosis and G1 arrest, wild-type p53 positively modulated the exit from the gamma-ray-induced G2 checkpoint. Taken together, these findings indicate that this new function for p53 is a component of the physiological pathway by which p53 exerts its role in apoptosis.

PMID: 7784074

1: *Exp Cell Res* 1996 Aug 1;226(2):292-301

IDEAL

DNA fragmentation induced by protease activation in p53-null human leukemia HL60 cells undergoing apoptosis following treatment with the topoisomerase I inhibitor camptothecin: cell-free system studies.

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We studied the role of proteases in apoptosis using a cell-free system prepared from a human leukemia cell line. HL60 cells are p53 null and extremely sensitive to a variety of apoptotic stimuli including DNA damage induced by the topoisomerase I inhibitor, camptothecin. We measured DNA fragmentation induced in isolated nuclei by cytosolic extracts using a filter elution assay. Cytosol from camptothecin-treated HL60 cells induced internucleosomal DNA fragmentation in nuclei from untreated cells. This fragmentation was suppressed by serine protease inhibitors. Serine proteases (trypsin, endoproteinase Glu-C, chymotrypsin A, and proteinase K) and papain by themselves induced DNA fragmentation in naive nuclei. This effect was enhanced in the presence of cytosol from untreated cells. Cysteine protease inhibitors (E-64, leupeptin, Ac-YVAD-CHO [ICE inhibitor]) did not affect camptothecin-induced DNA fragmentation. The apopain/Yama inhibitor, Ac-DEVD-CHO, and the proteasome inhibitor, MG-132, were also inactive both in the cell-free system and in whole cells. Interleukin-1 beta converting enzyme (ICE) or human immunodeficiency virus protease failed to induce DNA fragmentation in naive nuclei. Together, these results suggest that DNA damage activates serine protease(s) which in turn activate(s) nuclear endonuclease(s) during apoptosis in HL60 cells.

PMID: 8806433